PUBLISHED AND PUBLICLY AVAILABLE STUDIES ON REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF SILICONE MATERIALS RELEVANT TO GEL-FILLED BREAST IMPLANTS

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I. EXECUTIVE SUMMARY

The available data are consistent in showing that the silicone materials which are the same as, or similar to, those of mammary prostheses are neither reproductive toxicants nor teratogens in animals. The studies provide a substantial database from which the toxic potential of silicone can be assessed. As stated in the polydimethylsiloxane toxicity profile assessment by TNO BIBRA International Ltd., there is "no convincing evidence of reproductive toxicity in rats and rabbits".[1]

The literature contains some particularly well conducted and relevant studies addressing the issue of reproductive toxicity and teratogenic potential, such as the evaluations reported by Bates and coworkers and Siddiqui and coworkers. These investigations simulate the human route of exposure, examine dose-response effects, test the materials in more than one appropriate species, and are characteristic of state-of-the-art methods for developmental and reproductive toxicity testing.

For completeness, although the study designs are not directly relevant to implantable devices, this literature review includes investigations that utilized oral or inhalation administration of test compounds, typically at high exposure concentrations. As reported in several range finding inhalation reproductive studies performed during the mid-to-late 1990s under Dow Corning's Siloxane Research Program, male and female parental toxicity was associated with high exposure levels (generally 500 - 700 ppm) of aerosolized low molecular weight siloxanes (D_4 and D_5). Findings such as reduced parental food consumption and reduced live litter size were noted, although no adverse effects upon reproductive parameters such as mating indices, fertility indices, gestation and parturition were observed.

Although not included in this review, there are articles in the literature regarding the effects of phenylmethyl-substituted linear and cyclic siloxanes on the male and female reproductive systems. These studies have been excluded from this review since investigations of phenylmethyl-substituted linear and cyclic siloxanes are not considered pertinent to a discussion regarding gel-filled breast implants. Phenylmethyl-substituted siloxanes are not used in the manufacture of breast implants; polydimethylsiloxanes and diphenyldimethyl-substituted siloxanes are used in the manufacture of breast implants.

In conclusion, studies evaluating silicone elastomers are particularly relevant to the shell of mammary prostheses; whereas studies evaluating silicone gel, silicone fluid or low molecular weight silicones are more relevant to the silicone fill of gel-fill mammary prostheses. The studies in the literature demonstrate that no impairment of reproductive performance and no adverse effects on early development, including teratogenicity, result from subcutaneous implantation with silicone elastomer or gel associated with mammary prostheses. The conclusions drawn from the animal studies are further reinforced by the published clinical literature, in which there have been no reports of human birth defects or other reproductive effects associated with implantation of silicone mammary prostheses. Therefore, the weight of the evidence strongly indicates that silicone materials used in the manufacture of mammary prostheses are neither reproductive toxicants nor potential human teratogens.

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[1] Polydimethylsiloxane. Toxicity Profile. TNO BIBRA International Ltd. 1991.

II. REPRODUCTIVE AND DEVELOPMENTAL STUDIES OF SILICONE ELASTOMER

A. Summary

In a reproduction study in rats, subcutaneous implantation of two 1.2 cm silicone elastomer disks (~0.68 g/kg, equivalent to typical human exposure), 61 days (males) or 41 days (females) prior to mating, with sacrifice on either gestation day (GD) 20 or after delivery of pups, resulted in no maternal toxicity or adverse effects on fetal or neonatal viability or growth compared to controls. In a developmental study in rabbits, four 2.5 cm disks were implanted subcutaneously 42 days prior to insemination (estimated to equal 0.22 g/kg), with sacrifice of dams prior to delivery; no treatment-related maternal toxicity or developmental effects, including teratogenicity, were found.

Intrauterine implantation of miniature intrauterine devices composed of Silastic silicone elastomer (dimensions 3 mm x 1.5 mm) from GD 9 to 21 in rats resulted in decreased body weight in all implanted dams. In fetuses, increased early and late resorption rate, decreased mean litter size, and increased fetal anomalies were noted. In a separate experiment, sham-operated controls did not exhibit the increased malformation rate relative to untreated rats. The results from this study, however, should not be viewed as significant evidence that Silastic is teratogenic. While the sham operation procedures used in this study control for some of the stress and trauma associated with the surgical insertion of the rods, they do not control for possible physical effects exerted by foreign bodies inserted between pairs of implanted fetuses. Based on the design of this study, with the intrauterine implantation of silicone rods, it is obvious that these data are not particularly relevant to the potential exposure of a fetus to silicone mammary prostheses.

In conclusion, maternal exposure of rats and rabbits to silicone elastomer by subcutaneous implantation at doses up to 0.68 g/kg and 0.22 g/kg, respectively, prior to and during gestation, did not result in maternal toxicity, fetal toxicity, or teratogenicity. When silicone elastomer pieces were implanted directly into the uterine horn of pregnant rats, maternal and fetal toxicity occurred, most probably due to the physical presence of the implants.

B. Study Abstracts

1. **Schardein, J.L. 1991a. Developmental toxicity study in New Zealand white rabbits with silicone gel Q7-2159A and Silastic II mammary envelope elastomer implants (PMAA Report Reference 129, vol. 11). Dow Corning Tox. File No. 7376 and 7377.**

   Schardein, J.L. 1991b. One generation reproduction study in rats with silicone gel Q7-2159A and Silastic II mammary envelope elastomer implants (PMAA Report Reference 130, vol. 11). Dow Corning Tox. File No. (Pending).

Siddiqui, W.H., Schardein, J.L., Cassidy, S.L., and Meeks, R.G. 1994a. Reproductive and developmental toxicity studies of silicone elastomer Q7-2423/Q7-2551 in rats and rabbits. Fundam. Appl. Toxicol. 23:377-381.

Siddiqui, W.H. and Schardein, J.L. 1993. One generation reproduction study of silicone gel and Silastic II mammary envelope implants in rats. Toxicologist 13:75. (Abstract).

Material: Silicone elastomer breast implant envelope, Dow Corning (Q7-2423/Q7-2551).

Methods: Developmental toxicity. Groups of 25 female New Zealand white rabbits received four subcutaneous 2.5-cm discs of silicone elastomer (in two sites on each flank), while controls received polyethylene discs, 42 days prior to insemination. Dams were euthanized prior to delivery, and the offspring were evaluated for malformations and developmental variations.

Reproductive toxicity. Groups of 30/sex Charles River CD rats were implanted subcutaneously with two 1.2 cm discs of silicone elastomer (one in each flank), while controls received polyethylene discs, 61 days (males) or 47 days (females) prior to mating. On gestation day 20, approximately half the mated females were euthanized and the remaining females were allowed to deliver their litters. Litters were caged with their dams for 3 weeks after birth.

Results: Developmental toxicity. No maternal toxicity (clinical signs, body weight effects) or adverse developmental effects, including teratogenicity, were observed. A slight but statistically significant reduction in the number of live fetuses in the treated group occurred, but the value was within the mean of historical control values and was not considered biologically relevant.

Reproductive toxicity. No maternal toxicity (clinical signs, body weight effects), no impairment of reproductive performance, and no adverse effects on fetal development or neonatal viability or growth, resulted from implantation with elastomer.

Comments: These studies appear to have been well conducted. The size of the elastomer implants approximated the expected elastomer body burden of women with breast implants.

2. **Barlow, S.M. and Knight, A.F. 1983. Teratogenic effects of Silastic intrauterine devices in the rat with or without added medroxyprogesterone acetate. Fertil. Steril. 39:224-230.**

Material: Silicone elastomer; miniature intrauterine devices (IUDs) made from Silastic 382 Medical Grade Elastomer (Dow Corning Corporation), with and without approximately 2 mg medroxyprogesterone acetate (MPA)/IUD to simulate human devices. IUDs measured 3 mm x 1.5 mm.

Methods: On Gestation Day (GD) 9, pregnant female rats were randomly assigned to one of four groups: unoperated controls, sham controls (incision only), Silastic IUDs (one per uterine horn) without MPA, or Silastic IUDs with added MPA. Rats were sacrificed on GD 21, and live and dead fetuses were examined for weight, sex, gross abnormalities, and soft tissue or skeletal variations. This study was performed in two stages; sham-operated rats were included only in the second study.

Results: Body weight was significantly lower in all IUD implanted rat dams at GD 21, and upon necropsy all inserted IUDs were in place (in the uterine lumen). The body weight of the sham-operated dams was midway between Silastic exposed and unoperated controls, which implies that weight loss was associated with surgical trauma.

In fetuses, early (first experiment) and late (first and second experiments) resorption rates were significantly increased in the Silastic group compared to untreated controls. Mean live litter size was significantly reduced compared to untreated controls in the first experiment, but not the second experiment. Mean fetal weight was not affected. The prevalence of malformations was significantly increased in the Silastic group compared to unoperated controls (this occurred in both studies). Anomalies included subcutaneous hemorrhage, tracheobronchomegaly, displacement of the heart, abnormal sternal fusion, extra vertebrae, split centra, and short or extra ribs. The malformation rate in control rats that underwent sham operations was not significantly increased, compared with untreated control rats.

[The steroid, MPA, had other effects not discussed here (e.g., alteration in sex characteristics, masculinization of female fetuses and vice versa)].

Comments: This study provides evidence for maternal and fetal toxicity to intrauterine Silastic elastomer. However, the major flaw of this study could explain this finding; that is, there was no control for the physical presence of large objects in the uterus during fetal development. In a previous study, the authors reported no anomalies with a stainless steel device measuring 2

mm x 1 mm (somewhat smaller).[2] A size-matched control of this type is critical for this experiment.

C. References

Barlow, S.M. and Knight, A.F. 1983. Teratogenic effects of Silastic intrauterine devices in the rat with or without added medroxyprogesterone acetate. Fertil. Steril. 39:224-230.

Schardein, J.L. 1991a. Developmental toxicity study in New Zealand white rabbits with silicone gel Q7-2159A and Silastic II mammary envelope elastomer implants (PMAA Report Reference 129, vol. 11). Dow Corning Tox. File No. 7376 and 7377.

Schardein, J.L. 1991b. One generation reproduction study in rats with silicone gel Q7-2159A and Silastic II mammary envelope elastomer implants (PMAA Report Reference 130, vol. 11). Dow Corning Tox. File No. (Pending).

Siddiqui, W.H. and Schardein, J.L. 1993. One generation reproduction study of silicone gel and Silastic II mammary envelope implants in rats. Toxicologist 13:75.

Siddiqui, W.H., Schardein, J.L., Cassidy, S.L., and Meeks, R.G. 1994a. Reproductive and developmental toxicity studies of silicone elastomer Q7-2423/Q7-2551 in rats and rabbits. Fundam. Appl. Toxicol. 23:377-381.

[2] Barlow, S.M., and Knight, A.F., and House, I. 1981. Intrautrine exposure to copper IUDs and prenatal development in the rat. *J Reprod. Fertil.* 62:123.

III. REPRODUCTIVE AND DEVELOPMENTAL STUDIES OF SILICONE GEL

A. Summary

Subcutaneous implantation of approximately 0, 0.6, 7.3, or 14.8 g/kg silicone gel in female rats, one week before mating to gestation day (GD) 20, did not result in maternal or fetal toxicity, or teratogenicity.

Subcutaneous implantation of 0, 3, 10, or 30 mL/kg silicone gel in rats 61 days (males) or 41 days (females) prior to mating, and sacrifice at GD 20 or after delivery of pups did not result in any toxicity to the male rats, and no adverse effects were noted in reproductive performance. No adverse effects on fetal development, neonatal viability or growth were seen.

In conclusion, maternal exposure of rats and rabbits to silicone gel by implantation at doses up to 30 g/kg, prior to and during gestation, did not result in systemic or developmental effects, or impair reproductive performance.

B. Study Abstracts

1. Bates, H.K., Schulz, C.O., and Lee, C. 1993. Developmental toxicity evaluation of the mammary implant material, silicone gel P/N 3200, implanted subcutaneously in rats. Toxicologist 13:381. (Abstract).

Material: Silicone gel P/N 3200; source not specified.

Methods: Subcutaneous implantation of gel between scapulae of 40 virgin female Sprague-Dawley rats/group at least one week prior to a 4-day serial mating. Treatment of controls was not specified. Based on the body weight at the time of implantation, the average gel exposure was 0, 0.6, 7.3, or 14.8 g/kg. Signs of toxicity, food intake, and body weight were recorded. Animals were sacrificed on Gestation Day 20; maternal body and liver weight, implant status, fetal weight, sex, and morphological development were recorded.

Results: There were no adverse maternal or fetal effects observed. Specifically, no maternal lethality or signs of toxicity developed, nor was there any effect on maternal weight, liver weights, or pregnancy rates (pregnancy rates were actually higher in implanted animals). In fetuses, no effect was seen on post-implantation loss, mean fetal body weight/litter, or the prevalence of any malformations (external, visceral, or skeletal).

Comments: This study establishes a no-adverse-effect-level of 14.8 g/kg silicone gel for maternal and developmental toxicity in the rat, for gel implanted subcutaneously prior to pregnancy. This level is three times the EPA-recommended limit for oral exposure.

2. **Schardein, J.L. 1991a. Developmental toxicity study in New Zealand white rabbits with silicone gel Q7-2159A and Silastic II mammary envelope elastomer implants (PMAA Report Reference 129, vol. 11). Dow Corning Tox. File No. 7376 and 7377.**

Schardein, J.L. 1991b. One generation reproduction study in rats with silicone gel Q7-2159A and Silastic II mammary envelope elastomer implants (PMAA Report Reference 130, vol. 11). Dow Corning Tox. File No. (Pending).

Siddiqui, W.H., Schardein, J.L., Cassidy, S.L., and Meeks, R.G. 1994b. Reproductive and developmental toxicity studies of silicone gel Q7-2159A in rats and rabbits. Fundam. Appl. Toxicol. 23:370-376.

Siddiqui, W.H. and Schardein, J.L. 1993. One generation reproduction study of silicone gel and Silastic II mammary envelope implants in rats. Toxicologist 13:75.

Material: Silicone gel, Dow Corning (Q7-2159A).

Methods: Developmental toxicity. Groups of 25 female New Zealand white rabbits received 3, 10, or 30 ml/kg silicone gel subcutaneously in two flank sites, 42 days prior to insemination. Control animals received saline or CMC at the same sites. Test females were euthanized prior to delivery, and offspring were evaluated for malformations or developmental variations.

Reproductive toxicity. Groups of 30/sex Charles River CD rats were implanted subcutaneously (in two flank sites) with 3, 10, or 30 ml/kg silicone gel, 61 days (males) or 47 days (females) prior to mating. Controls received either saline or carboxymethylcellulose (CMC) at the same sites. On GD 20, approximately half the mated females were euthanized, the remaining pregnant females were allowed to litter. Litters were caged with their dams for 3 weeks following birth.

Results: Developmental toxicity. No maternal toxicity (clinical signs or fertility effects) or fetal developmental effects, including teratogenicity, were observed.

Reproductive toxicity. No maternal toxicity (clinical signs, body weight effects, or fertility effects) or adverse effects on fetal development and neonatal viability and growth were observed. One male each in the CMC and low-dose groups died, but the deaths were not considered to be related to treatment; no clinical signs of toxicity were observed in males.

Comments: Administration of the test article did not result in developmental toxicity or adversely affect reproductive performance in rats. No maternal or developmental effects, including teratogenicity, were observed in rabbits. The highest dose was selected on the basis of likely human body burden.

C. References

Bates, H.K., Schulz, C.O., and Lee, G. 1993. Developmental toxicity evaluation of the mammary implant material, silicone gel P/N 3200, implanted subcutaneously in rats. Toxicologist 13:381.

Schardein, J.L. 1991a. Developmental toxicity study in New Zealand white rabbits with silicone gel Q7-2159A and Silastic II mammary envelope elastomer implants (PMAA Report Reference 129, vol. 11). Dow Corning Tox. File No. 7376 and 7377.

Schardein, J.L. 1991b. One generation reproduction study in rats with silicone gel Q7-2159A and Silastic II mammary envelope elastomer implants (PMAA Report Reference 130, vol. 11). Dow Corning Tox. File No. (Pending).

Siddiqui, W.H. and Schardein, J.L. 1993. One generation reproduction study of silicone gel and Silastic II mammary envelope implants in rats. Toxicologist 13:75.

Siddiqui, W.H., Schardein, J.L., Cassidy, S.L., and Meeks, R.G. 1994b. Reproductive and developmental toxicity studies of silicone gel Q7-2159A in rats and rabbits. Fundam. Appl. Toxicol. 23:370-376.

IV. REPRODUCTIVE AND DEVELOPMENTAL STUDIES OF SILICONE FLUID

A. Summary

Studies to assess the reproductive or developmental effects of silicone fluid have been conducted using subcutaneous, oral, and dermal routes of exposure. The subcutaneous exposure studies are the most relevant with respect to the potential mode of absorption of silicone fluid after breast implantation, and they contain the best data set in terms of well-designed, well-conducted and well-reported studies.

By subcutaneous administration, PDMS was evaluated for developmental and reproductive toxicity in rats at dose levels up to 20 g/kg/day in a study by Bates et al. (1985) and in rats and rabbits at dose levels up to 1000 mg/kg/day in studies by Kennedy et al. (1976), Jackson and Kennedy (1967), and Kennedy (1967). The study design by Bates et al. (1985) is very applicable to evaluating the safety of silicone breast implants. No dose- or treatment-related maternal or fetal toxicity, or teratogenicity was found. Because no maternal or fetal toxicity was evident, the question may be raised as to whether sufficiently high doses were used to adequately evaluate the teratogenic potential of PDMS. It should be noted, however, that the high dose administered in this study (20 g/kg/day) approximates the amount of exposure that would be expected if two implants containing silicone gel ruptured during the organogenic period in a woman. This study supports the finding that silicone materials are not teratogenic in animals.

Kennedy et al. (1976), Jackson and Kennedy (1967) and Kennedy (1967) evaluated the effects of selected polydimethylsiloxanes (PDMS) on reproduction and fetal development in both rats and rabbits using a protocol patterned after FDA guidelines for a three-segment reproduction and teratology study. The first set of studies was conducted at the Food and Drug Research Laboratories (FDRL) using standard Segment I, II, and III tests. In a second set of studies, similar Segment I, II, and III protocols were used and the experiments were conducted at Industrial Bio Test (IBT)[2].

In the work conducted at FDRL, the Phase I study of PDMS (DC 360 fluid) in rats showed no adverse effects on fertility, resorption incidence, gestation length, pup viability or lactation indices. No gross abnormalities were seen. In Phase II studies of PDMS (DC 360 fluid), no adverse effects in rabbit fetuses were seen on weight or development, however, in rats, a slight increase in skeletal variations at 1000 mg/kg/day was seen. Inadequate data on maternal toxicity prevent a complete analysis of the contribution of adverse maternal effects to this finding. No adverse developmental effects were seen in rats at doses at or below 200 mg/kg/day. A dose-related increase in the incidence of *in utero* mortality was observed for the group of rats treated with 200 and 1000 mg/kg/day (DC 360 fluid) in the Segment III study (A replication of this study at IBT did not corroborate this finding).

Both the DC 700 fluid and DC 225 fluid proved to be non-teratogenic in the rat

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[2] It should be noted that the FDA has disqualified all IBT studies, and IBT data therefore would not be considered acceptable unless validated.

and rabbit in studies conducted at IBT (Kennedy et al. 1976). A rabbit teratology study conducted at IBT (Jackson and Kennedy 1967) found an increase in fetal resorptions at subcutaneous doses ≥200 mg/kg. Phase I, II, and III studies in rats conducted at IBT (1967) found no treatment-related effects with subcutaneous doses up to 1000 mg/kg/day.

The developmental or reproductive effects of PDMS were also investigated by the dermal route of exposure. Doses of PDMS up to 200 mg/kg/day in Phase II studies of rabbits (Kennedy et al. 1976; Jackson and Kennedy 1967; Jackson 1966; Jackson and Kennedy 1966) did not result in treatment-related teratogenic effects with the exception of a high incidence of resorptions noted in the study by Jackson and Kennedy (1966). This study was conducted at IBT. In another study conducted by IBT, male rabbits treated dermally with 200 mg/kg/day of various PDMS fluids for 28 days exhibited no adverse effects on testicular weight or spermatogenesis (Hobbs et al. 1972). Male rabbits treated dermally with 3000 mg/kg/day of PDMS did not have any adverse effects on semen, spermatogenesis, or reproductive organ weights (Campbell and Seawall 1969). In a study conducted at IBT, male monkeys dosed dermally with 2000 mg DC 360/kg/day for 27 months showed no adverse systemic or reproductive effects. When mated to untreated females, offspring did not demonstrate any abnormalities (Kime 1968).

No treatment-related embryotoxicity, fetotoxicity, or teratogenicity was seen from dietary administration of up to 2.5% Antifoam A, or oral gavage of 1000 mg DC 700/kg/day to rabbits in Phase II studies. No treatment-related effects of various silicone fluids were seen on male reproductive organs in rats exposed to 1000 mg/kg/day for 28 days or 3.3 ml/kg/day for 7 days.

In conclusion, animal exposure to levels of PDMS that are many orders of magnitude greater than the maximum exposure hypothesized to occur from gel bleed from two silicone gel-filled mammary implants (maximum exposure is calculated as 3.2 grams over the period of 20 years), did not result in adverse reproductive and developmental effects.

B. Study Abstracts

1. **Bates, H.K., Cunny, H.C., and Laborde J.B. 1991. Developmental toxicity evaluation of polydimethylsiloxane injection in the Sprague-Dawley rat. Paper presented at symposium, Silicone in Medical Devices, 1-2 February, Baltimore, Maryland.**

   Bates, H., Filler, R., and Kimmel, C. 1985. Developmental toxicity study of polydimethylsiloxane injection in the rat. Teratology 31:50A.

Material: Polydimethylsiloxane (PDMS) fluid, Dow Corning 360 fluid (viscosity 350 cs).

Methods <u>Preliminary Study</u>. A preliminary study was conducted to aid in the selection of dose levels and experimental design for the definitive study.

Two dosing regimens were used. Sprague-Dawley female rats (10/group) were injected subcutaneously with 0.85 percent saline controls, 0.5, 1, or 2 g/kg/day of PDMS from Gestation Day (GD) 6 to 15. Separately, 10 female rats/group received a single subcutaneous injection of saline, 5, 10, or 20 g/kg of PDMS one week prior to mating. Dams were allowed to deliver pups and rear for 4 days. Pups were counted and examined.

Definitive Study. Groups of 24 female rats were administered 0.85 percent saline, 1, 10, or 20 g/kg body weight of PDMS one week prior to mating. Dams were euthanized on GD 20, and uteri were examined. Fetuses were also sacrificed and examined for visceral and skeletal malformations.

Results: Preliminary Study. The only notable finding in this study was an increased rate of post-implantation loss in the groups receiving a single injection of 5 or 10 g/kg of PDMS. The response observed in the high-dose group (20 g/kg) was similar to controls.

Definitive Study. No maternal or fetal toxicity was observed with PDMS treatment. No treatment-related effect on post-implantation loss was observed. PDMS was not teratogenic under the conditions of the study.

Comments: This study was well designed and appropriately conducted and reported. The significance of the increased incidence of post-implantation loss in the preliminary study is questionable since there was no dose-response relationship and the finding was not repeated in the definitive assay. PDMS was not teratogenic under the conditions of the assay. A brief review of silicone fluid developmental toxicity studies in animals is also provided in the report.

2. **Kennedy, G.L., Keplinger, M.L., Calandra, J.C., and Hobbs, E.J. 1976. Reproductive, teratologic, and mutagenic studies with some polydimethylsiloxanes. J. Toxicol. Environ. Health 1:909-920.**

Carson, S. 1967. Studies of the effects of Dow Corning 360 medical grade fluid (MDX-4-4011) on reproduction in rats and rabbits (PMAA Report Reference 46, vol. 3). Dow Corning Tox. File No. 1059-4.

Material: Polydimethylsiloxane fluids, Dow Corning 360 medical grade fluid (360 centistokes); Dow Corning 700 vapor booster pump fluid (7 centistokes); Dow Corning 225 fluid (10 centistokes).

Methods: DC 360.

Phase I – rat: Rats were subcutaneously administered 0, 20, or 200 mg/kg PDMS (controls received sesame oil). Males received 3 injections/week for 10 weeks prior to mating, and females received 7 injections/week for 2 weeks prior to mating. Half of the dams were sacrificed on Gestation Day (GD) 13, while the remaining females delivered pups and reared to 21 days postpartum. Dams and pups were necropsied. Indices of fertility, gestation, viability and lactation were calculated.
Phase II – rat: Pregnant rats were administered 0, 20, 200, or 1,000 mg/kg subcutaneously on GD 6 to 16 (controls received sesame oil); on GD 20, dams were sacrificed and fetuses examined for abnormalities.
Phase II – rabbit: Pregnant rabbits were given 0, 20, 200, or 1,000 mg/kg subcutaneously on GD 6 to 18; on GD 29, the dams were sacrificed and fetuses examined for abnormalities.
Phase III – rat: Pregnant females were given 0, 20, 200, or 1,000 mg/kg subcutaneously from GD 15 through Day 21 postpartum (controls received sesame oil). On Day 21 postpartum, pups and dams were necropsied. Dams were evaluated for body weight, behavior, length of gestation, and gross abnormalities at sacrifice; pups were evaluated for body weight, viability, and gross abnormalities at sacrifice.

DC 700 and DC 225. Tested for teratogenicity according to protocol in Phase II above, except DC 700 administered by gavage and DC 225 by dermal exposure.

DC 700. Dominant lethal test, male mice were given a single 0, 5, or 10 mg/kg, intraperitoneal dose. At weekly intervals for 6 weeks, males were mated to females. Mutation rates were determined by the number of resorptions and viable embryos.

Results: The Phase I study in the rat showed no effect of PDMS on fertility. There was no reported treatment-related toxicity to the male rats. Incidence of resorptions, gestation length, pup viability, and lactation indices (survival to 21 days) were comparable in treated groups and controls. No gross abnormalities were observed in treated animals.

Developmental (Phase II) studies in rats showed no treatment related effects on incidence of resorptions, viability or fetal weight. Skeletal examinations revealed increased variations in the fetuses from the 1000 mg/kg dose group (no statistical analysis available). There was no reported maternal toxicity; however, data were inadequate for complete analysis.

In the Phase II study in rabbits, two animals at each of the higher dose

levels died during pregnancy. No other data to evaluate maternal toxicity were presented. There were fewer live pups per litter in all treated groups compared with control; however, there was no apparent dose-response. Resorptions were reported to be slightly greater in treated animals; however, they were within historical control limits and not considered to be related to treatment. *In utero* mortality was greater in all treated groups than control, however, no dose response was apparent and this effect was reported to be within the historical control limits. No effects on fetal weight or development were reported.

In the Phase III study, one female each in the low- and high-dose groups died, apparently from a respiratory infection. No adverse effect of PDMS treatment was seen on maternal body weight, and no adverse effects on reproductive performance were noted. Mean body weights of pups and gestation, viability and lactation indices were comparable between treated and control animals. The only significant exposure-related finding was an increase in *in utero* mortality in the 200 and 1000 mg/kg dose groups. This study was repeated by IBT and the finding of increased *in utero* mortality was not corroborated.

DC 700 and DC 225 were not teratogenic in a study conducted by IBT. DC 700 was not mutagenic in the dominant lethal test in mice conducted by IBT. Based on these results, silicones were not considered reproductive toxicants.

Comments: As noted previously, the FDA has disqualified all IBT studies, and IBT data therefore would not be considered acceptable unless validated. Furthermore, data interpretation for these studies is difficult due to the lack of statistical analysis of the data and inadequate measurements of maternal toxicity. PDMS did not appear to be teratogenic under the conditions of the studies. Some skeletal variations and increased *in utero* mortality may have been the result of maternally toxic doses. No reproductive or teratologic effects were seen in any of the studies at 20 mg/kg/day.

3. Jackson, G.L., and Kennedy, G. 1967. Rabbit teratology study: TX-114 (PMAA Report Reference 45, vol. 3). Dow Corning Tox. File No. 1059-3.

Material: Polydimethylsiloxane fluid; 360 Medical fluid (350 cs.) [TX-114].

Methods: Pregnant New Zealand albino rabbits (15 animals/group) were dosed from Gestation Days (GD) 6 to 18 with silicone fluid or sesame oil control (200 mg/kg dermally; 20, 200, or 1000 mg/kg subcutaneously). There was also

an untreated control group. Dams were evaluated for body weight, total implantation sites, resorptions, and normal and abnormal young, while pups were examined for gross abnormalities, 24-hour viability (respiratory and paw movements), and skeletal malformations.

Results: No treatment-related effects on maternal body weight or behavior were observed. An increase in fetal resorptions was observed for both subcutaneous test and vehicle control groups; the increase was directly related to the total amount of material administered, as compared to the untreated control. There was also an increase in fetal resorptions in the dermal test and control groups compared to the untreated control. Fetal resorptions appeared to be increased in the test groups given 200 or 1000 mg/kg subcutaneously compared to their respective vehicle controls. Dermal application did not appear to increase resorptions over the vehicle control values. Skeletal abnormalities were observed in pups of animals dosed with 200 mg/kg dermally and subcutaneously. The frequency of malformations, however, was reported to be consistent with the historical control of the laboratory. Furthermore, no malformations were observed in pups from the highest dose group. A slight reduction in 24-hour viability was observed in the 1000 mg/kg test group; however, this was reported to be within historical control limits.

Comments: The data from this IBT study suggest that increased fetal resorptions occur with subcutaneous doses ≥200 mg/kg. Skeletal abnormalities were not dose-related and were within historical control range.

4. Kennedy, G. 1967. Reproduction study, albino rats, TX-114 (PMAA Report Reference 47, vol. 3). Dow Corning Tox. File No. 1059-5.

Material: Polydimethylsiloxane fluid; 200 fluid (350 cs.) [TX-114].

Methods: Phase I: Male and female albino rats were subcutaneously dosed with 20, 200, or 1000 mg/kg/day of test material or sesame oil control for 102 and 101 days, respectively. Select male and female animals were sacrificed on Gestation Day (GD) 14 and examined pathologically. In newborns, lactation ability and pup weight, external condition, and viability were recorded.

Phase II: Pregnant albino rats were dosed subcutaneously on GD 6 to 15, with equivalent test materials. On GD 20 animals were sacrificed and dams were examined for copra lutea, implantation sites, and viable fetuses, while pups underwent external, visceral, and skeletal examination.

Phase III: Pregnant albino rats were dosed subcutaneously from GD 15 through lactation with equivalent test materials. Data regarding maternal growth, mortality, and reactivity and progeny number, survival, growth, and pathology were recorded.

Results: Phase I: No treatment-related effects were reported for any of the parameters measured.

Phase II: No treatment-related effects were reported for any of the parameters measured.

Phase III: No treatment-related effects were reported for any of the parameters measured.

Comments: These results from this IBT study indicate that subcutaneous treatment with up to 1000 mg/kg of TX-114 has no reproductive, teratogenic, or perinatal and postnatal adverse effects. No raw data were reported, however.

5. **Kime, J. 1968. Dermal toxicity of DC 555 fluid and DC 360 fluid, 350 cs., with regard to the reproductive capacity of the primate (PMAA Report Reference 48, vol. 3). Dow Corning Tox. File No. 1059-9.**

Material: Polydimethylsiloxane fluid; 360 Medical Fluid (350 cs.).

Methods: Male monkeys *(Macaca speciosa)* were dosed dermally with 0 or 2000 mg/kg/day (5 days/week) PDMS for 27 months. Treatment of controls was not specified. Following treatment, the animals were mated with untreated females. The following data were collected during the study: food consumption, body weight, testicular biopsies and measurements, semen evaluation, reproductive capacity, infant behavior and body weights, and histopathology of adult males and infants. Hematology, clinical chemistry, and urinalyses were conducted at months 7 and 20.

Results: No abnormalities were reported for any of the parameters measured.

Comments: The results from this IBT study indicate that dermal exposure to 2000 mg/kg/day (5 days/week) PDMS for 27 months has no adverse systemic or reproductive effects. No raw data, however, were included with this report. The number of animals tested was not indicated.

6. Hobbs, E.J., Fancher, O.E., and Calandra, J.C. 1972. Effect of selected organopolysiloxanes on male rat and rabbit reproductive organs. Toxicol. Appl. Pharmacol. 21:45-54.

Material: Polydimethylsiloxane (PDMS) fluid 200, 550, 556, 704, 1107, FS-1265 fluids (Dow Corning) of varying viscosities. This study also looked at dimethylphenylmethylcyclosiloxane, which is not found in saline-filled or silicone gel-filled breast implants.

Methods: Male rabbits (10/group) were treated dermally with 200 mg/kg/day of DC 200, 550, 556, or FS-1265 for 28 days. Male rats (10/group) received oral doses of 3.3 mL/kg/day of DC 200, 550, 556, 704, 1107, or FS-1265 for 7 days. Control animals (10/group) received saline. Assays for testicular atrophy and reduced testicular function were performed.

Five human volunteers were exposed dermally to Dow Corning 200, 556, and FS-1265 fluids at 50 mg/kg/day for 20 hours/day for 10 days and were tested for abnormal silicon levels in both blood and urine at various time points during the trial.

Results: PDMS fluids 200, 550, 556, 704, 1107, and FS-1265 did not produce changes in rabbit testicular weight or spermatogenesis after dermal exposure, or seminal vesicle weight in rats after oral exposure. Monitoring of blood and urine levels suggested that there was no apparent absorption of silicon in humans exposed dermally.

Comments: Data from the human study were not included in the report. This study was conducted by IBT.

7. Campbell, A.H., and Sewell, W.R. 1969. Effects of three silicones (Dow Corning 556 fluid, Dow Corning 360 medical fluid, 350 cs., and Dow Corning MDX 4-4122) on the reproductive organs of male rats and rabbits (PMAA Report Reference 49, vol. 3). Dow Corning Tox. File No. 1059-30.

Material: Polydimethylsiloxane (PDMS) fluid; 556 Cosmetic Grade fluid, 360 medical fluid (350 cs.), and MDX 4-4122 silicone fluid (Dow Corning).

Methods: Male Sprague-Dawley rats (n=50) and male albino rabbits (n=25) were each divided into five groups and dosed daily (5 days/week) for 4 weeks with test or control materials.

Rats. (10 animals/group) were dosed orally with 1000 mg/kg/day of 556 silicone fluid, 360 silicone fluid, MDX 4-4122 silicone fluid, or tap water.

Body weight, food consumption, water consumption, behavior, and general health were monitored throughout the study. After 4 weeks, animals were sacrificed and gross pathology and male reproductive organ weight were recorded.

Rabbits. Rabbits (5 animals/group) were dosed dermally for 6 to 7 hours/day for 4 weeks with 3 mL (3000 mg/kg/day) of 556 silicone fluid, 360 silicone fluid, MDX 4-4122 silicone fluid, or distilled water. Body weights and semen samples were collected weekly. Semen samples were evaluated for volume, viscosity, color, sperm quantity, sperm motility, and sperm morphology. After 4 weeks, animals were sacrificed and male reproductive organs were weighed.

Results: Rats. No signs of systemic toxicity were reported in any animals. No treatment-related effects on absolute or relative weights of testes, epididymides, or prostates were seen.

Rabbits. No treatment-related abnormalities in semen volume, color or viscosity, or sperm counts, motility or morphology were noted. Weights of testes, epididymides, prostates or seminal vesicles were not affected by test article treatment.

Comments: These data indicate a lack of test article toxicity on the male reproductive endpoints measured.

8. Jackson, G.L. 1966. Rabbit teratology study TX-135B (PMAA Report Reference 44, vol. 3). Dow Corning Tox. File No. 1056-2.

Material: Polydimethylsiloxane (PDMS) fluid; 200 fluid (10 cs.) [TX-135B].

Methods: Two groups of 10 pregnant rabbits were dosed dermally with 200 mg/kg PDMS suspended in corn oil from Gestation Days (GD) 6 to 18; controls received corn oil alone. A third group of 10 served as an untreated control. On GD 29, animals were sacrificed and dams were evaluated for total implantation sites and resorptions; pups were evaluated for gross abnormalities, 24-hour viability (respiratory and paw movements), and skeletal malformations.

Results: No treatment-related effects on maternal body weight were observed. A slight increase in resorptions was observed in the test group (8 percent of implantation sites), as compared to the vehicle control group (3 percent of implantation sites). These findings, however, were within the normal control range of the laboratory. Clubbing of the extremities was noted in

one test group pup. However, it was concluded that there were no treatment-related effects on external or internal development of the fetuses or on 24-hour viability, as compared to the control.

Comments: This study was conducted by IBT. No statistical analysis was presented.

9. Jackson, G.L., and Kennedy, G. 1966. Rabbit teratology study: TX-114 (PMAA Report Reference 43, vol. 3). Dow Corning Tox. File No. 1059-2.

Material: Polydimethylsiloxane fluid; 360 Medical Fluid (350 cs.) [TX-114].

Methods: Two groups of 10 pregnant rabbits were dosed dermally with 200 mg/kg silicone fluid suspended in corn oil from Gestation Days (GD) 6 to 18; controls received corn oil alone. A third group of 10 served as an untreated control. On GD 29, animals were sacrificed and dams were evaluated for total implantation sites and resorptions; pups were evaluated for gross abnormalities, 24-hour viability (respiratory and paw movements), and skeletal malformations.

Results: No treatment-related effects on maternal body weight were observed. Six of the ten test females had one or more resorptions. A total of 11 resorptions of 89 total implantations (12 percent) were observed in the test group, as compared to the vehicle control and untreated control groups (5 percent and 3 percent resorptions, respectively). Of the test fetuses surviving on day 29, 3/78 displayed gross abnormalities. One fetus from each control group (number of animals not given) had umbilical hernia. Skeletal examination revealed three fetuses with abnormalities in the test group and none in the controls. No effects on 24-hour viability were observed in any of the pups.

Comments: The data from this IBT study indicate that TX-114 produces a high incidence of resorptions in treated females at dermal doses of 200 mg/kg (12 percent), compared to the historical range of the laboratory (0 to 7 percent). Complete data were not presented and no statistical analysis was done.

10. Siddiqui, W.H., Stanton, E., Kolesar, G.B., and Devries, C.R. 1985. Teratogenic potential of Dow Corning Antifoam A compound food grade in rabbits. Report submitted to the Environmental Protection Agency, Document No. 878215093.

Material: Antifoam A compound, food grade (Dow Corning).

Methods: Dietary Antifoam A was administered to pregnant New Zealand white rabbits in feed at levels of 0, 0.5, 1.0, or 2.5 percent from Gestation Days 6 through 19. Dams were observed for signs of toxicity, body and liver weight, and resorptions. Fetuses were examined for external, visceral, or skeletal abnormalities after birth.

Results: No treatment-related maternal toxicity (signs and symptoms of toxicity or fertility effects) or embryotoxicity, fetotoxicity, or teratogenicity was seen.

Comments: This study supports the lack of reproductive or developmental effects of Antifoam A at dietary doses as high as 2.5 percent, which is 2,500 times higher than levels normally consumed. Antifoam A is commonly used in food processing as an anti-foam agent at levels to 10 ppm.

C. References

Bates, H., Filler, R., and Kimmel, C. 1985. Developmental toxicity study of polydimethylsiloxane injection in the rat. Teratology 31:50A.

Bates, H.K., Cunny, H.C., and Laborde J.B. 1991. Developmental toxicity evaluation of polydimethylsiloxane injection in the Sprague-Dawley rat. Paper presented at symposium, Silicone in Medical Devices, 1-2 February, Baltimore, Maryland.

Campbell, A.H., and Sewell, W.R. 1969. Effects of three silicones (Dow Corning 556 fluid, Dow Corning 360 medical fluid - 350 cs., and Dow Corning MDX4-4122) on the reproductive organs of male rats and rabbits (PMAA Report Reference 49, vol. 3). Dow Corning Tox. File No. 1059-30.

Carson, S. 1967. Studies of the effects of Dow Corning 360 medical grade fluid (MDX-4-4011) on reproduction in rats and rabbits (PMAA Report Reference 46, vol. 3). Dow Corning Tox. File No. 1059-4.

Hobbs, E.J., Fancher, O.E., and Calandra, J.C. 1972. Effect of selected organopolysiloxanes on male rat and rabbit reproductive organs. Toxicol. Appl. Pharmacol. 21:45-54.

Jackson, G.L. 1966. Rabbit teratology study TX-135B (PMAA Report Reference 44, vol. 3), Dow Corning Tox. File No. 1056-2.

Jackson, G.L., and Kennedy, G. 1966. Rabbit teratology study: TX-114 (PMAA Report Reference 43, vol. 3). Dow Corning Tox. File No. 1059-2.

Jackson, G.L., and Kennedy, G. 1967. Rabbit teratology study: TX-114 (PMAA Report Reference 45, vol. 3). Dow Corning Tox. File No. 1059-3.

Kennedy, G. 1967. Reproduction study, albino rats, TX-114 (PMAA Report Reference 47, vol. 3). Dow Corning Tox. File No. 1059-5.

Kennedy, G.L., Keplinger, M.L., Calandra, J.C., and Hobbs, E.J. 1976. Reproductive, teratologic, and mutagenic studies with some polydimethylsiloxanes. J. Toxicol. Environ. Health 1:909-920.

Kime, J. 1968. Dermal toxicity of DC 555 fluid and DC 360 fluid, 350 cs. with regard to the reproductive capacity of the primate (PMAA Report Reference 48, vol. 3). Dow Corning Tox. File No. 1059-9.

Siddiqui, W.H., Stanton, E., Kolesar, G.B., and Devries, C.R. 1985. Teratogenic potential of Dow Corning Antifoam A compound, food grade in rabbits. Report submitted to the Environmental Protection Agency, Document No. 878215093.

V. REPRODUCTIVE AND DEVELOPMENTAL STUDIES OF LOW MOLECULAR WEIGHT SILICONES

A. Summary

Exposure of rats and rabbits by inhalation to 0, 100, 300, or 700 ppm D_4 (equivalent to 0, 1,215, 3,644, and 8,505 mg/m^3) or 0, 100, 300 or 501 ppm D_4 (equivalent to 0, 1,215, 3,644, and 6,075 mg/m^3), respectively, during gestation days (GD) 6 to 18 did not result in adverse developmental effects, fetal toxicity, or teratogenicity, even at levels that caused significant reductions in maternal body weight in rats (700 ppm) (York and Schardein 1994).

In a range-finding study, oral exposure of female rabbits to 0, 50, 100, 500, or 1,000 mg/kg/day D_4 by gavage on GD 7 to 19 resulted in decreased food consumption (statistically significant at ≥500 mg/kg) and decreased maternal body weight at all dose levels (statistical significance not reported). A statistically significant increase in fetal abortions was noted at doses above 500 mg/kg.

The reproduction toxicity studies associated with the Dow Corning Siloxane Research Program (reports available from Dow Corning on CD-ROM) included six inhalation range-finding studies administering D_4 or D_5. These were followed by an inhalation reproductive toxicity study of D_4 using multiple exposure regimens and a two generation study of D_5. Parental toxicity was associated with the inhalation of high test article concentrations (generally 500 - 700 ppm). Findings included reductions in body weight, food consumption, mean number of implantations, and mean live litter size. Exposure to high concentrations of D_4 in female rats during different phases of their reproductive cycle demonstrated that the reduction in intrauterine survival which was observed when exposure was initiated prior to mating and continued into gestation was reversible when exposure was discontinued three days prior to mating. Furthermore, intrauterine survival was also not adversely affected when test article exposure occurred after the mating period, from gestation day 2 to gestation day 5. Based on the two generation inhalation study, the no-observed-adverse-effect level (NOAEL) for D_5 is 160 ppm.

In a study by Hobbs and Olsen (1971) evaluating acute toxicological properties, the reproductive parameter measured was seminal vesicle organ weight. Oral exposure of male rats to 4 mL/kg/day (approximately 4 g/kg/day) did not result in adverse effects on seminal vesicle weight. No dominant lethal effects were detected after gavage administration of up to 1000 mg/kg/day D_4 for 8 weeks to male rats (Isquith et al. 1982).

In conclusion, exposure to low molecular weight silicones by the oral route did not result in adverse developmental effects at doses which were not maternally toxic. Exposure by inhalation did not result in adverse developmental effects even at dose levels which resulted in significant maternal toxicity.

B. Study Abstracts

1. York, R. and Schardein, J.L. 1994. Developmental toxicity studies with octamethylcyclotetrasiloxane (D_4) in CD rats and rabbits. Toxicologist 14:572. (Abstract)

Material: Low molecular weight silicone, octamethylcyclotetrasiloxane (OMCTS, or D_4) (manufacturer unspecified).

Methods: Pregnant CD rats and New Zealand white rabbits (30 females/group and 20 females/group, respectively) were exposed by inhalation to 0, 100, 300, or 700 ppm D_4 (equivalent to 0, 1,215, 3,644, and 8,505 mg/m^3, respectively) or 0, 100, 300 or 501 ppm D_4 (equivalent to 0, 1,215, 3,644, and 6,075 mg/m^3, respectively) for 6 hours/day on GD 6 to 18. On GD 20 (rats) or 29 (rabbits), cesarean sections were performed and fetuses were observed for developmental effects (malformations) and survival. Maternal observations included clinical signs of toxicity, and measurement of body weight and food intake.

Results: Significant maternal weight loss occurred at the highest dose in the rat but not the rabbit, and food intake was decreased in both the rat and rabbit at this dose. No developmental toxicity (malformations or variations) occurred at any dose in rats or rabbits.

Comments: Inhalation of D_4 at levels up to 501 ppm in the rabbit or 700 ppm in the rat did not result in any adverse developmental effect in fetuses, even at a maternally toxic dose in the rat.

2. Dow Corning. 1992. Preliminary information from a range-finding developmental study in rabbits in octamethylcyclotetrasiloxane. Dow Corning Report submitted to the Environmental Protection Agency, Document No. OTS-0515093-4.

Material: Low molecular weight silicone, octamethylcyclotetrasiloxane (OMCTS, or D_4) (Dow Corning Corporation).

Methods: This range-finding study was conducted to establish doses for a forthcoming developmental study. Pregnant white rabbits (6 females/groups) were administered 0, 50, 100, 500, or 1000 mg/kg/day D_4 by oral gavage for Gestation Days 7 to 19. Observations included clinical signs of toxicity, and maternal body weight, food intake, and fetal survival.

Results: Maternal weight loss occurred at all doses tested (statistical significance not reported), along with statistically significant decreased food intake at the two highest dose levels, and a statistically significant number of fetal abortions at doses ≥500 mg/kg. One dam at the 500 mg/kg dose level died. The maternal toxicity was cited as the cause for the decreased fetal survival.

Comments: Fetal toxicity occurred at maternally toxic doses.

3. **Stump A.S., 1996a. An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Rats, Dow Corning Report No. 1995-I0000-40919**

Stump A.S., 1996b. An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Rats, Dow Corning Report No. 1996-I0000-41337

Material: Low molecular weight silicone, octamethylcyclotetrasiloxane (D_4).

Methods: Initial Study

Groups of Sprague-Dawley Crl:CD®BR rats (20/sex/group) were exposed by inhalation to 0, 70, or 700 ppm D_4 for 6 hours/day for 28 days prior to mating and through the mating period. Exposure for the females continued to lactation day 21, except when discontinued from gestation day 21 through lactation day 4. F_0 females were necropsied either after being allowed to deliver and rear their pups to lactation day 21 or 27 days following the mating period (no litter delivered). F_0 males were necropsied after the mating period. On post natal day 21, surplus F_1 pups were necropsied. From post natal day 21 to 28, selected F_0 pups in the test article groups were exposed by inhalation to the test article, then necropsied. Parameters evaluated included body weight gain, food consumption, fertility indices, mating indices, pup viability indices, pup sex ratios and necropsy findings.

Repeat Study

Groups of Sprague-Dawley Crl:CD®BR rats (22/sex/group) were exposed by inhalation to 0 or 700 ppm D_4 for 6 hours/day for 28 days prior to mating and through the mating period. Exposure for the females continued to gestation day 20. F_0 females were necropsied either after being allowed to deliver and rear their pups to post natal day 4 or 25 days following the mating period (no litter delivered). F_0 males were

necropsied after the mating period. Parameters evaluated included body weight gain, food consumption, fertility indices, mating indices, pup viability indices, pup sex ratios and necropsy findings. In addition, testes and epididymides from males and ovaries from females were weighed and examined microscopically. Spermatogenic endpoints were evaluated for males.

Results: Initial Study

Test article related observations included dried material around the nose and eyes in both F_0 males and F_0 females of the high dose group. An increased incidence of ejaculatory plugs was found in association with the high dose male rats. In addition, inhibition of body weight gain was observed in the high dose males and females. Reduction of food consumption was also observed in the female rats. No internal findings related to test article exposure were observed in the males during necropsy. Reproductive parameters including days between pairing and coitus, mating indices, fertility indices, gestation and parturition were not adversely affected by exposure to the test article. The mean number of implantation sites was reduced and the mean live litter size was reduced in the 700 ppm group. No adverse test article-related effects on F_1 pup sex ratios, viability indices, or internal findings were observed.

Repeat Study

Test article related observations included dried material around the nose for the F_0 males and F_0 females of the exposure group. In addition, brown vaginal discharge in the females and an increased incidence of ejaculatory plugs in the males was associated with test article exposure. Mean body weight and food consumption were reduced in the females. No exposure related internal findings were observed in the males during necropsy. Reproductive parameters including days between pairing and coitus, mating indices, fertility indices, gestation and parturition were not adversely affected by exposure to the test article. Two females in the test article group had total litter loss; the finding was not considered test article related. The mean number of implantation sites and corpora lutea were reduced, whereas the mean number of sites unaccounted and pre-implantation loss were increased in the test article group. No exposure related findings were associated with the ovaries, testes and epididymides regarding organ weights or microscopic tissue evaluation. Mean live litter size and pup viability indices were reduced in the 700 ppm group but were within range of the laboratory's historical control values. F_1 pup sex ratios, pup weight, and clinical and necropsy observations were not adversely affected by exposure to the test article.

Comments: Parental toxicity was associated with the inhalation of D_4 at 700 ppm as observed from reductions in body weight and food consumption. Exposure to 700 ppm of D_4 was related to a statistically significant reduction in the mean number of implantation sites and the mean live litter size. Other study parameters were not adversely affected by exposure to the test article.

In the repeat study, parental toxicity was observed in the 700 ppm test article group. A decrease in number of implantation sites and corpora lutea, and an increase in pre-implantation loss and numerical difference between the number of implantation sites and the number of offspring were observed. There was also a reduction in mean live litter size and pup viability indices.

4. **Stump A.S., 1997a. An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Rats, Dow Corning Report No. 1997-I0000-42936**

Kaufman, L.E., 1997. An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Rats, Dow Corning Report No. 1997-I0000-43725

Stump A.S., 1997b. An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Rats, Dow Corning Report No. 1997-I0000-43726

Material: Low molecular weight silicone, octamethylcyclotetrasiloxane (D_4).

Methods: Females Rat Study

Groups of Sprague-Dawley rats (22 females/group) were exposed by inhalation to 0, 70, 300, 500, or 700 ppm D_4 for 6 hours/day for at least 70 days before mating. Exposure continued to lactation day 21, except when discontinued from gestation day 21 through lactation day 4. Male rats were not exposed to the test article and were discarded after the mating period. F_0 females were necropsied either after being allowed to deliver and rear their pups until lactation day 21 or 25 days following the mating period (no litter delivered). From post natal day 21 to 28, F_1 selected pups in the test article groups were exposed by inhalation to the test article, then necropsied. Parameters evaluated included body weight gain, food consumption, fertility indices, mating indices, pup viability indices, pup sex ratios and necropsy findings. Selected organs were weighed and

selected tissues were examined microscopically from F_0 females and F_1 weanlings. Ovarian follicle counts were also obtained from F_0 females.

Male Rat Study

Groups of Crl:CD®(SD)BR rats (22 males/group) were exposed by inhalation to 0, 70, 300, 500, or 700 ppm D_4 for 6 hours/day for 70 days before mating and throughout the mating period. Female rats were not exposed to the test article. Females were necropsied either after being allowed to deliver and rear their pups until lactation day 4 or 25 days following the mating period (no litter delivered). F_1 pups were necropsied on lactation day 4. Males were either necropsied soon after mating ended and had only a short non-exposure period (week 12 necropsy) or they were necropsied approximately one month after mating ended and had a non-exposure period of several weeks (week 15 - 16 necropsy). Parameters evaluated included body weight gain, food consumption, mating indices, fertility indices, pup viability indices, pup sex ratios and necropsy findings. In addition, selected organs from F_0 males necropsied at 12 weeks were weighed and selected tissues were examined microscopically; sperm motility and morphology were also evaluated.

Repeat Male Rat Study

Groups of Sprague-Dawley rats (40 males/group) were exposed by inhalation to 0, 500, or 700 ppm D_4 for 6 hours/day for 70 days before mating, during the mating period and through study day 113. Prior to necropsy, F_0 males had a non-exposure period of approximately 5 weeks. F_0 female rats were not exposed to the test article. Females were necropsied either after being allowed to deliver and rear their pups to lactation day 21 or 25 days following the mating period (no litter delivered). Parameters evaluated included body weight gain, food consumption, mating indices, fertility indices, pup viability indices, pup sex ratios and necropsy findings. In addition, selected organs from F_0 males were weighed.

Results:

Female Rat Study

Estrous cyclicity, days between pairing and coitus, mating indices, fertility indices, gestation and parturition were not adversely affected by test article exposure. Exposure-related clinical signs in the F_0 females of the 300, 500 and 700 ppm groups included red material around the eyes and nose. Reduction in mean body weight gain was also observed in the 500 and 700 ppm groups. In the high dose group, the mean number of implantation sites was reduced and the numerical difference between the

number of implant sites and the number of offspring was increased. No test article related findings were noted regarding follicle counts or microscopic evaluation of selected tissues. Mean liver weights were increased at the 300, 500 and 700 ppm exposure levels. Mean live litter size and mean number of pups born were reduced in the high dose group. Mean pup weight, pup survival, and percentage of males per litter were unaffected. No exposure-related findings associated with organ weights or microscopic tissue evaluations were observed in the F_1 pups.

Male Rat Study

Treatment-related clinical signs in the F_0 males included red material around the nose in the 700 ppm exposure group. In addition, increased numbers of ejaculatory plugs were observed in all exposure groups. Mean body weight, body weight gain and food consumption were not affected by exposure to the test article. Reproductive parameters including days between pairing and coitus, mating indices, fertility indices, gestation and parturition were not adversely affected by exposure to the test article. No internal findings related to test article exposure were noted in males during necropsy. No adverse exposure-related findings were noted during the microscopic tissue evaluations or the sperm motility and sperm morphology evaluations. In the 12 week necropsies, liver weights were increased in the 500 and 700 ppm exposure groups, in addition to increased kidney and thyroid gland weights in the 700 ppm group. In the 15 - 16 week necropsies, no effects on organ weights were noted, indicating that the increases observed at the 12 week interval were reversible. A slight reduction in pup survival was noted in the high dose group but this finding was confounded by the reduction being primarily associated with two litters. Mean pup weights were reduced in the high dose group, but were within the historical control data range of the test facility. Mean live litter size and pup sex ratios were unaffected by exposure to the test article. No exposure-related clinical or necropsy findings were noted in the F_1 pups.

Repeat Male Rat Study

An increased incidence of dried red material around the nose was noted in F_0 males in the 700 ppm group. In addition, a dose related increase in the incidence of ejaculatory plug formation was observed in the 500 and 700 ppm groups. Mean body weight gain and food consumption was reduced in the 700 ppm group males. No exposure-related necropsy findings were observed. Organ weights were unaffected by test article exposure. Reproductive parameters including days between pairing and coitus, mating induces, fertility indices, gestation and parturition were not

adversely affected by exposure to the test article. Mean live litter size, number of pups born, percentage of males per litter at birth, pup survival and mean pup body weights were unaffected in the test article groups. No exposure-related necropsy findings were noted in the F_1 pups.

Comments: Maternal toxicity was demonstrated in the F_0 females at test article exposure levels of 300, 500 and 700 ppm by clinical signs and at 500 and 700 ppm by reductions in mean body weight gain. Mean liver weights were increased in the F_0 females at 300, 500 and 700 ppm exposure levels. Findings which included reductions in mean live litter size, in the number of pups born, and in the number of implantation sites were noted in the 700 ppm group. Postnatal toxicity (F_1 pups) was not observed at exposure levels of 70, 300 or 500 ppm.

F_0 male toxicity was observed at the 700 ppm exposure level. Slight toxicity was also observed in the males at 500 ppm. No adverse effects on F_1 pups were observed except for reduced pup survival and body weights at the 700 ppm exposure level. The interpretation of these findings were confounded by the reduced pup survival occurring primarily in two litters and the mean pup weights being within the historical control data range of the test facility.

Toxicity was demonstrated in the F_0 males at an exposure level of 700 ppm by clinical signs and by reduced body weight gain and food consumption. No adverse effects were noted on F_1 pups in the 500 or 700 ppm groups.

5. **Stump A.S., 1996a. An Inhalation Range-Finding Reproductive Toxicity Study of Decamethylcyclopentasiloxane (D5) in Rats, Dow Corning Report No. 1996-I0000-41336**

Stump D.G., 1999. A Two-Generation Inhalation Reproductive Toxicity and Developmental Neurotoxicity Study of Decamethylcyclopentasiloxane (D5) in Rats, Dow Corning Report No. 1999-I0000-46098

Material: Low molecular weight silicone, decamethylcyclotetrasiloxane (D_5).

Methods: Range-finding Study

Groups of Sprague Dawley Crl:CD®BR rats (22/sex/group) were exposed by inhalation to 0, 26, and 132 ppm D_5 for 6 hours/day for 28 days prior to mating and through the mating period. Exposure for the females continued to lactation day 21, except when discontinued from gestation

day 21 through lactation day 4. F_0 females were necropsied either after being allowed to deliver and rear their pups to post natal day 21 or 25 days following the mating period (no litter delivered). F_0 males were necropsied after the mating period ended. From post natal day 21 to 28, pups in the test article groups were exposed by inhalation to the test article, then necropsied. Parameters evaluated included body weight gain, food consumption, mating indices, fertility indices, gestation, parturition, pup viability indices, pup sex ratios and necropsy findings.

Two-generation Study

Groups of Crl:CD®(SD)BR rats (30/sex/group) were exposed by inhalation to 0, 30, 70, or 160 ppm D_5 for 6 hours/day for 70 days prior to mating. Exposure for F_0 and F_1 males continued throughout mating until the day before euthanization. Exposure for the F_0 and F_1 females continued throughout mating and gestation until gestation day 20. Then exposure to the F_0 and F_1 females was reinitiated on lactation day 5 and continued until the day before euthanization. Body weight and food consumption data were collected.

F_0 females were allowed to deliver and rear their pups until weaning on lactation day 21. F_0 parental animals and surplus F_1 pups were necropsied and selected organs weighed. Offspring (30/sex/group) from the F_0 generation were selected to constitute the F_1 generation. The selected F_1 animals were evaluated for balanopreputial and vaginal patency (developmental landmarks). Subsequently, the F_1 generation was allowed to mate and the F_1 females to deliver and rear their pups (F_2 generation) until weaning on lactation day 21. Functional observational battery evaluations were performed on F_1 females on gestation day 10 and lactation day 20. In the high dose and control groups, spermatogenic evaluations of F_0 and F_1 males, as well as ovarian primordial follicle and corpora lutea counts for F_0 and F_1 females, were performed. Thirty pups/sex/group from the F_2 generation were selected for developmental analyses (including neurobehavorial testing, neuropathology brain weights and/or brain dimension measurements, as well as evaluation for balanopreputial and vaginal patency). F_1 parental and non-selected F_2 pups were necropsied and selected organs weighed.

Results: Range-finding Study

Reproduction parameters including days between pairing and coitus, mating, fertility, gestation and parturition were not adversely affected by test article exposure. In the high dose group, two F_0 females had total litter loss. This finding was considered equivocal and best resolved in the

two-generation study. Mean body weights, body weight gain and food consumption were unaffected by exposure to the test article. No internal findings related to the test article were observed during the necropsies. The numerical difference between the mean number of implantation sites and the number of offspring was not adversely affected by exposure to the test article. No exposure-related effects were observed regarding mean live litter size, number of dead pups on post natal day 0, pup viability (with the possible exception of the two total litter losses, as previously discussed), pup sex ratios and mean pup weight. No exposure-related clinical signs or necropsy findings were noted for the F_1 pups.

Two-generation Study

A few mortalities occurred in the F_0 test article groups but no clear exposure-response relationship for the mortalities was evident and no consistent target organ was identified. All F_1 parental animals survived to scheduled necropsy and no exposure-related clinical findings were observed. Reproductive parameters (days between pairing and coitus, mating indices, fertility indices, duration of gestation, and parturition) in the F_0 and F_1 generations were not adversely affected by test article exposure. In addition, body weights, body weight gains, and food consumption in the F_0 and F_1 generations were not adversely affected by test article exposure. Functional observational battery data for the F_1 females revealed no exposure-related effects.

No exposure-related gross necropsy or organ weight findings were noted in the F_0 and F_1 animals. Increased indices of minimal alveolar histiocytosis were noted in F_0 females, F_1 males and F_1 females in the three test article concentration groups compared to the control group. The finding was not associated with histopathological lung lesions or differences in lung weights, therefore, this finding was considered a compensatory response to the inhalation route of test article administration. F_0 and F_1 mean ovarian primordial follical counts, and spermatogenic endpoints were not affected by test article exposure.

F_1 and F_2 mean live litter size, number of pups born, pup sex ratio, post natal survival, and anogenital distances were not affected by parental exposure to the test article. One F_0 female had a total litter loss (a one pup litter) in the high dose group. The single occurrence was not attributed to test article exposure. Mean pup body weight, physical condition, necropsy findings, pup organ weights and developmental landmarks in the F_1 and F_2 pups were not attributed to parental test article exposure.

Comments: Inhalation of D_5 at levels of 26 and 132 ppm in the rat did not result in

adverse parental toxicity or reproductive effects. No adverse effects on F_1 pups were observed although two females in the high dose group had total litter loss. This finding was considered equivocal and best resolved in the two-generation study.

No parental toxicity in the F_0 and F_1 generations was observed in the test article exposure groups. Reproductive performance was not affected. No neonatal toxicity was observed in the F_1 and F_2 generations. No developmental neurotoxicity was evident at any test article concentration. Based on this study, the no-observed-adverse-effect level (NOAEL) for parental toxicity, reproductive toxicity, neonatal toxicity and developmental neurotoxicity is considered to be 160 ppm.

6. Kaufman, L.E., 1998. An Inhalation Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D4) in Rats Using Multiple Exposure Regimens, Dow Corning Report No. 1998-I0000-44490

Material: Low molecular weight silicone, octamethylcyclotetrasiloxane (D_4).

Methods: Groups of Sprague-Dawley Crl:CD®(SD)BR female rats were exposed by inhalation to D_5 for 6 hours/day during different phases of their reproductive cycles. In the Overall Phase portion of the study, female rats were exposed for 28 days prior to mating, through the mating period and into gestation until gestation day 19. In the Ovarian Phase portion of the study, female rats were exposed from 31 days prior to the start of the mating interval until three days prior to the start of mating. In the Fertilization Phase portion of the study, female rats were exposed to test article from three days prior to the start of the mating, through the mating interval and into gestation until gestation day 3. In the Implantation Phase portion of the study, female rats were exposed from gestation day 2 through gestation day 5. The test article concentrations selected for the Overall Phase were 70, 300, 500 and 700 ppm (24 females per concentration). Only one test article concentration, 700 ppm, was selected for the Ovarian Phase (60 females), Fertilization Phase (60 females) and Implantation Phase (24 females). Control female rats and all male rats were not exposed to the test article.

Clinical observations, body weights, and food consumption were recorded. All males and females without evidence of mating were euthanized following completion of breeding. Mated females were euthanized on gestation day 20. Uteri and ovaries were examined, and the number of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Mean gravid uterine weights and net body weight changes

were calculated. Brain, ovaries, adrenal glands, and thyroid glands from females were weighed at scheduled necropsy.

In addition, satellite females from the Overall Phase, Fertilization Phase and Implantation Phase were exposed to 700 ppm test article. Clinical observations, body weights, food consumption data and liver weights were recorded and blood, perirenal fat and liver samples were collected.

Results: Exposure to the test article did not adversely effect reproductive parameters including days between pairing and coitus, mating indices and fertility indices. There was one unscheduled delivery in an exposure group; the event was not attributed to the test article. At necropsy, mean adrenal gland weight was increased in the Overall Phase for animals exposed to 700 ppm test article and mean absolute ovarian weight was reduced in the Fertilization Phase for animals exposed to 700 ppm. No decrease in ovarian weight was observed in the Overall, Ovarian and Implantation Phases. Reduced body weight gains or mean body weight losses in each Phase were noted in the animals exposed to 700 ppm test article. Reduced body weight gain or body weight loss were also observed in some animals exposed to the 300 and 500 ppm concentration levels. Reduced food consumption, reduced mean gravid uterine weights and decreased viable litter sizes were associated with the body weight findings.

In the Overall Phase, intrauterine survival was adversely affected by test article exposure at 500 and 700 ppm. In addition, there were reductions in mean absolute numbers of implantation sites and the number of viable fetuses. An increase in mean pre-implantation losses was also noted at the 500 and 700 ppm exposure levels. Mean post-implantation loss was increased at the 700 ppm concentration, whereas mean numbers of corpora lutea were decreased at the 300, 500 and 700 ppm exposure levels.

In the Fertilization Phase, intrauterine survival was adversely affected by exposure to 700 ppm test article. Mean numbers of implantation sites, mean number of corpora lutea, and number of viable fetuses were reduced, whereas mean pre-implantation loss and post-implantation loss were increased.

Intrauterine survival and mean number of corpora lutea were unaffected by test article exposure in the Ovarian and Implantation Phases

Comments: Maternal toxicity was evident at exposure levels of 300, 500 and 700 ppm by inhibition of body weight gain and reduced food consumption. Reduced numbers of implantation sites and viable fetuses were noted in animals exposed to 500 and 700 ppm test article. Reduced numbers of corpora lutea were observed in animals exposed to 300, 500 and 700 ppm

test article. Increased mean pre-implantation losses were noted with exposure to 500 and 700 ppm test article and an increase in mean post-implantation losses was observed with exposure to 700 ppm test article.

The effects of intrauterine survival noted following test article exposure for three days prior to mating until gestation day 3 were similar to the effects noted following test article exposure for 28 days prior to mating until gestation day 19. However, intrauterine survival was not adversely affected when test article exposure was terminated three days prior to mating, indicating the reversibility of these responses. Intrauterine survival was also not adversely affected when test article exposure occurred after the mating period, from gestation day 2 to gestation day 5.

7. **Hobbs, E.J., and Olsen, K. 1971. Acute toxicological properties, industrial hazards and rat seminal vesicle (RSV) effects of Dow Corning F 1-3597 (PMAA Report Reference 11, vol. 1). Dow Corning Tox. File No. 1723-1.**

Material: Mixed cyclic low molecular weight siloxanes (see below).

Methods:

Acute Toxicity. Rats (2/sex) dosed orally with 20 g/kg of DC-345 (relative percents as follows: 71.9 D_5; 21.9 D_6; 4.0 D_7; 1.3 D_8; 0.6 D_9; 0.2 D_{10}; 0.1 D_{11}; 0.58 percent linears, and trace amounts of D_3 and D_4).

Eye Irritation. Rabbits received undiluted DC-345 in left and right eyes. Left eye was washed after exposure.

Skin Irritation. DC-345 was applied on the ear, abdomen, and abraded abdomen of rabbits.

Subacute Oral Toxicity. Ten male rats were dosed orally by gavage with 4 mL/kg DC-345 for 5 days. Seminal vesicle weights were recorded.

Results: There were no deaths reported at an acute dose of 20 g/kg. Eye irritation was very slight. Slight conjunctivitis resolved by 24 hours. Skin irritation tests produced no effects. There was no effect on seminal vesicle organ weight.

Comments: Seminal vesicle organ weight was the only reproductive parameter measured. No adverse effects were noted on this endpoint at an oral dose of 4 mL/kg.

8. Isquith, A.J., Siddiqui, W.H., Miller, B.J., and Stanton, E. 1982. Evaluation of octamethylcyclotetrasiloxane in the rodent dominant lethal assay (PMAA Report Reference 54, vol. 4). Dow Corning Tox. File No. 1362-9.

Material: Low molecular weight silicone, octamethylcyclotetrasiloxane (D_4).

Methods: In a dominant lethal assay, male rats were dosed with 0, 100, 500, or 1,000 mg/kg/day D_4, by oral gavage for a period of 8 weeks prior to mating. Treated males were mated to undosed females; dams were sacrificed 14 days from the mid-week of mating and the numbers of corpora lutea and live and dead implantations were counted. Body weight and fertility were evaluated in the males.

Results: No statistically significant reduction in fertility was found in any of the treated groups, as compared to the negative control. No effect on body weight of males was noted due to treatment. No treatment related effects on other reproductive parameters (corpora lutea, total implants, pre-implantation loss, dead implants, live implants) were noted.

Comments: This study examined the fertility of female rats as indicators of clastogenic activity (chromosomal damage) in the germinal tissue of the treated males following exposure to D_4. There was no evidence of genetic activity or adverse effects on the reproductive parameters measured.

C. References

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Stump A.S., 1997a. An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D_4) in Rats, Dow Corning Report No. 1997-I0000-42936

Stump A.S., 1997b. An Inhalation Range-Finding Reproductive Toxicity Study of Octamethylcyclotetrasiloxane (D_4) in Rats, Dow Corning Report No. 1997-I0000-43726

Stump D.G., 1999. A Two-Generation Inhalation Reproductive Toxicity and Developmental Neurotoxicity Study of Decamethylcyclopentasiloxane (D_5) in Rats, Dow Corning Report No. 1999-I0000-46098

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VI. CONCLUSION

As the range-finding studies have demonstrated, high doses of low molecular weight siloxanes, when administered by inhalation or oral gavage, can cause parental toxicity. However, when animals were exposed to similarly administered lower doses, toxicity was not observed.

In consideration of gel-filled breast implants, the available data indicate that silicone materials which are the same as, or similar to, those used in the manufacture of mammary prostheses are neither reproductive toxicants nor teratogens in animals. The studies demonstrate that no impairment of reproductive performance and no adverse effects on fetal development, including teratogenicity, result from subcutaneous implantation with silicone elastomer or gel. Therefore, the weight of the evidence strongly indicates that silicone materials used in the manufacture of mammary prostheses are neither reproductive toxicants nor human teratogens.

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